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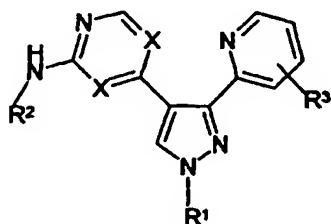
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: PYRAZOLES AS TGF INHIBITORS

WO 02/062787 A1



(I)

(57) Abstract: Therapeutically active pyrazole derivatives of formula (I) wherein R¹-R³ are as defined in the specification, processes for the preparation thereof, the use thereof in therapy, particularly in the treatment of prophylaxis of disorders characterised by overexpression of transforming growth factor β (TGF- β), and pharmaceutical compositions for use in such therapy.

PYRAZOLES AS TGF INHIBITORS

5 The present invention relates to novel pyrazole derivatives, processes for the preparation thereof, the use thereof in therapy, particularly in the treatment or prophylaxis of disorders characterised by overexpression of transforming growth factor β (TGF- β), and pharmaceutical compositions for use in such therapy.

10 TGF- β is a multi-functional cytokine which belongs to the TGF- β superfamily which includes activins/inhibins, bone morphogenetic proteins (BMPs) and TGF- β s. Three isoforms of TGF- β (TGF- β 1, TGF- β 2, and TGF- β 3) have been identified in mammals, each of which is encoded by a distinct gene on different chromosomes (D.A. Lawrence, *Eur. Cytokine. Netw.*, 1996, 7(3), 363). TGF- β initiates an intracellular signalling pathway which ultimately leads to the expression of genes that regulate cell cycle, control proliferative responses, or relate to extracellular matrix proteins that mediate cell adhesion, migration and intercellular communication. TGF- β has pleitropic effects including modulation of cell growth and differentiation, extracellular matrix formation, hematopoiesis, and immunomodulation (Roberts and Spoon, *Handbook of Experimental Pharmacology*, 1990, 95, 419-458).

25 A variety of cell surface proteins and receptors are known to transduce the signals initiated by the binding of the active TGF- β ligand to its receptors. Initiation of the TGF- β signalling pathway results from the binding of the TGF- β ligand to the extracellular domain of the type II membrane receptor (Massague, *Ann. Rev. Biochem.*, 1998, 67, 753.). The bound type II receptor then recruits type I (Alk5) receptor into a multimeric membrane complex, whereupon active type II receptor kinase phosphorylates and activates type I receptor kinase. The function of the type I receptor kinase is to phosphorylate a receptor-associated co-transcription factor, Smad-2 or Smad-3; 30 thereby releasing it into the cytoplasm where it binds to Smad-4. The PAI-1 gene is activated by TGF- β as a consequence of the abovementioned cellular pathway.

35 One approach to the treatment and/or prophylaxis of disorders characterised by the overexpression of TGF- β is inhibition of the TGF- β signal transduction. For example, inhibition of the TGF- β type II receptor by overexpression of a dominant negative TGF- β

type II receptor has previously been shown to prevent liver fibrosis and dysfunction in rat models (*Proc. Natl. Acad. Sci.*, 1999, **96**(5), 2345), and also to prevent progression of established liver fibrosis (*Hepatology*, 2000, **32**, 247).

5 Pathological overexpression of TGF- β is known to be associated with a number of undesirable effects, leading ultimately to the development of serious pathogenic conditions (G.C. Blöbe *et al.*, *N. Engl. J. Med.*, 2000, 1350). In particular, pathological overexpression of TGF- β may cause excessive accumulation of extracellular matrix (ECM), inhibition of cell proliferation and immunosuppression. Excessive accumulation 10 of ECM is known to lead to fibrotic diseases such as tumor fibrosis, radiation-induced fibrosis, fibrosis of the liver, kidney, lung, bowel, heart, pancreas, peritoneum or other organs. Fibrosis can lead to pathologic conditions such as cirrhosis, idiopathic pulmonary fibrosis, glomerulosclerosis and hypertrophic scars.

15 A number of other disease states are known to be associated with variations in the expression of genes which are controlled by TGF- β including cancer development, abnormal bone function and inflammatory disorders.

20 The development of compounds capable of inhibiting the TGF- β intracellular pathway is seen as a desirable way to effect prophylaxis and/or treatment of the above-mentioned conditions. Compounds capable of inhibiting the TGF- β intracellular pathway and/or the expression of TGF- β may be used in the treatment of disorders the symptoms of which often lead to the development of fibrotic conditions. For example, compounds of the 25 present invention may be useful in treating the fibrosis associated with various liver-related conditions such as hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-induced hepatitis, haemochromatosis and primary biliary cirrhosis.

30 The compounds of the present invention are pyrazole derivatives. Other pyrazole compounds have previously been described for use in alternative medicinal applications. PCT Patent Applications, WO 96/03385, WO 98/52937, WO 98/52940, WO 98/52941 and WO 00/31063 (Searle & Co) disclose a series of substituted pyrazole compounds and their use in the treatment of p38 kinase mediated disorders. In particular the compounds described are useful in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis and asthma.

European Patent Application No. 0 846 687 (Lilly & Co) describes novel substituted pyrazoles useful for the inhibition of sPLA₂ mediated release of fatty acids. Such compounds are useful in the treatment of conditions such as septic shock. EP 0 846 686 (Pfizer Ltd) discloses a series of condensed pyrazole derivatives which act as 5 inhibitors of both Interleukin-1 (IL-1) and tumor necrosis factor (TNF). Such compounds are useful in the treatment of IL-1 and TNF mediated diseases such as chronic inflammatory diseases, specific autoimmune disease and sepsis-induced organ injury. None of the aforementioned patent applications describe the pyrazole compounds of the present invention.

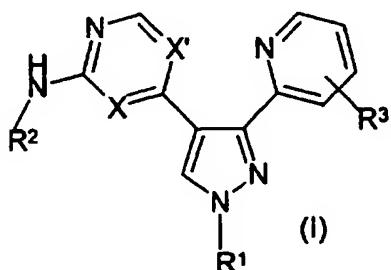
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PCT Patent Application WO 00/12947 (Scios Inc.) describes the use of a series of quinazoline derivatives for treating various disorders associated with enhanced activity of kinase p38- α and/or TGF- β . The compounds described therein have been shown to inhibit the activities of both proteins and are therefore particularly useful for the 15 treatment of conditions in which an enhanced activity towards both p38- α and TGF- β is required.

20

It has now been discovered that certain substituted pyrazole compounds, as described below, are useful in the treatment or prophylaxis of disorders characterised by the overexpression of TGF- β . In particular, compounds of the present invention are TGF- β inhibitors which act at the TGF- β type I (Alk5) receptor.

According to one aspect of the present invention, we provide compounds of formula (I).



25

wherein,

R¹ is selected from H, C₁₋₄ alkyl or CH₂CONR⁴R⁵;

R² is selected from -(CH₂)_n-phenyl, -(CH₂)_n-heterocycl, -(CH₂)_n-heteroaryl, each of which may be further substituted by one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁₋₄ alkyl or C₁₋₄ alkoxy, -NO₂, -NH₂, -NR⁴R⁶, -CONR⁴R⁶, -NHCOR⁴, -SO₂R⁴, -SO₂NHR⁴, -O(CH₂)_nNR⁴R⁶;

R³ is selected from H, halo (such as fluoro, chloro, bromo), -CN, -CF₃, C₁₋₄ alkyl or C₁₋₄ alkoxy;

R⁴ is selected from H or C₁₋₄ alkyl;

R⁵ is C₁₋₄ alkyl;

R⁶ is selected from heterocycl or heteroaryl;

or R⁴R⁶ together with the nitrogen atom to which they are attached form a 3, 4, 5, 6 or 7 membered saturated or unsaturated ring which may additionally contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁₋₄ alkyl and C₁₋₄ alkoxy;

n is 0, 1, 2, 3, 4 or 5;

X and X', which may be the same or different, are each selected from CH or N, provided that X and X' are not both N;

and salts and solvates thereof (hereinafter "compounds of the invention").

As used herein the term "alkyl" as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing the specified number(s) of carbon atoms. Such alkyl groups in particular include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl and hexyl.

The term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy and *tert*-butoxy.

5 The term "heterocyclyl" as a group or part of a group refers to a stable saturated or partially saturated (i.e. non-aromatic) 3 to 6 membered monocyclic ring containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur, optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁-₄ alkyl and C₁-₄ alkoxy.

10 The term "heteroaryl" as a group or part of a group refers to a stable heterocyclic aromatic 6 to 14 membered monocyclic ring containing one or more hetero atoms independently selected from nitrogen, oxygen and sulfur, optionally substituted with one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁-₄ alkyl and C₁-₄ alkoxy.

15 The present invention also covers the physiologically acceptable salts of the compounds of formula (I). Suitable physiologically acceptable salts of the compounds of formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di- basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like.

20 The present invention also relates to solvates of the compounds of formula (I), for example hydrates.

25 Compounds of formula (I) wherein R¹ is H may exist in tautomeric forms. The individual tautomers and mixtures thereof are included within the scope of the present invention.

30 Preferably, R¹ is H or C₁-₄ alkyl, more preferably R¹ is H.

Preferably, n is 0 or 1.

Preferably, R² is -(CH₂)_n-phenyl or -(CH₂)_n-heterocyclyl. More preferably, R² is -(CH₂)_n-phenyl or -(CH₂)_n-heterocyclyl substituted by one or more substituents selected from

5 halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CONR⁴R⁶, -SO₂R⁴ or -O(CH₂)_nNR⁴R⁶. Most preferably, n is 0 and R² is phenyl substituted by one or more substituents selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁₋₄ alkyl, C₁₋₄ alkoxy, -CONR⁴R⁶, -SO₂R⁴ or -O(CH₂)_nNR⁴R⁶ and n is 1; or n is 1 and R² is furanyl.

10

Preferably, R³ is located at the C(3) or C(6) position of the pyridine ring and is selected from H, halo (such as fluoro, chloro, bromo), -CN, -CF₃, C₁₋₄ alkyl or C₁₋₄ alkoxy. More preferably, R³ is H or alternatively C₁₋₄ alkyl. Most preferably, R³ is H.

15

Preferably R⁴ and R⁶ together with the nitrogen atom to which they are attached represent pyrrolidine, pyrrolidine, imidazole, N-substituted imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, piperidine, morpholine, thiomorpholine, piperazine, N-substituted piperazine.

20

More preferably R⁴ and R⁶ together with the nitrogen atom to which they are attached represent pyrrolidine, piperidine, morpholine, piperazine, N-substituted piperazine (preferably N-methyl-piperazine), imidazole, or N-substituted imidazole (preferably N-methyl-imidazole).

25

It will be appreciated that the present invention is intended to include compounds having any combination of the preferred groups as listed hereinbefore.

Compounds of formula (I) which are of special interest as agents useful in the treatment or prophylaxis of disorders characterised by the overexpression of TGF- β are:

30

(4-Chlorophenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;

Phenyl-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;

(4-Fluoro-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;

Furan-2-ylmethyl-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;

(3-Methanesulfonyl-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;

35

3-[4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-amino]-benzonitrile;

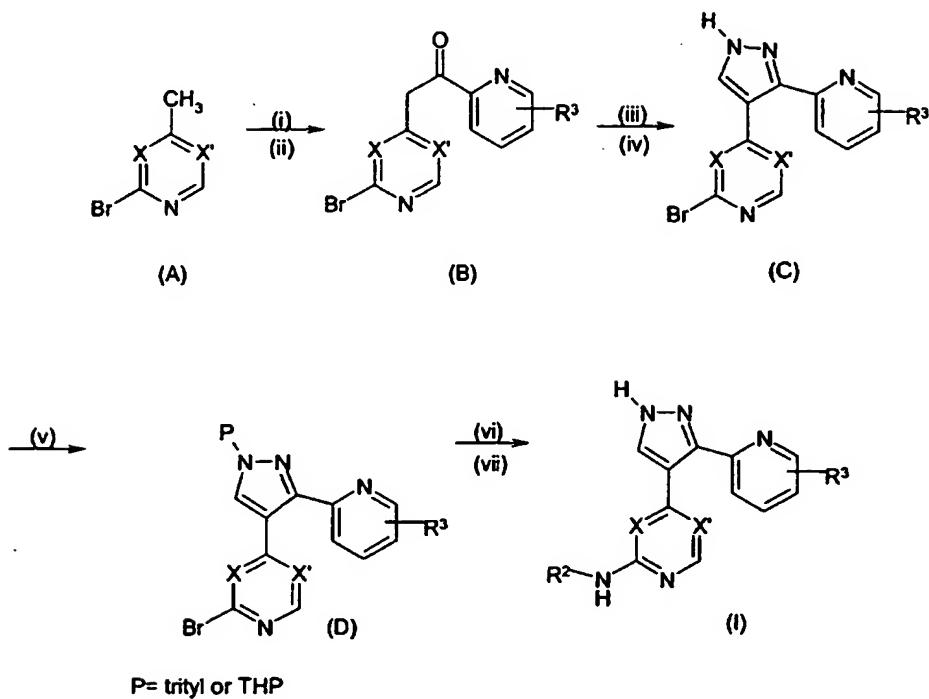
2-Methoxy-4-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-amino]-benzonitrile;
[4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-[3-(2-piperidin-1-yl-ethoxy)-phenyl]-
amine;
[4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-[3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-
5 amine;
(3-Chloro-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-*m*-tolyl-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-
amine;
10 (3,4-Dimethoxy-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
(4-Chloro-3-methyl-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
2-Chloro-5-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-benzonitrile;
4-[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-phenol;
15 (4-Methoxy-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-*p*-tolyl-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-[3-trifluoromethoxy-phenyl]-amine;
(3,4-Dimethyl-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-[4-trifluoromethyl-phenyl]-amine;
15 (3-Isopropoxy-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
20 (4-Methanesulfonyl-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
2-Methoxy-4-[4-(3-(6-methyl-pyridin-2-yl)-1H-pyrazol-4-yl)-pyridin-2-ylamino]-
benzonitrile;
Morpholin-4-yl-[4-[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-
phenyl]-methanone;
25 (4-Methyl-piperazin-1-yl)-[4-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-
phenyl]-methanone;
[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-
amine; and
[3-(1-Methyl-1H-imidazol-2-ylmethoxy)-phenyl]-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-
30 pyridin-2-yl]-amine;
and salts and solvates thereof.

Compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

Compounds of formula (I) may conveniently be prepared according to the general methodologies in Schemes 1, 2 and 3 below:

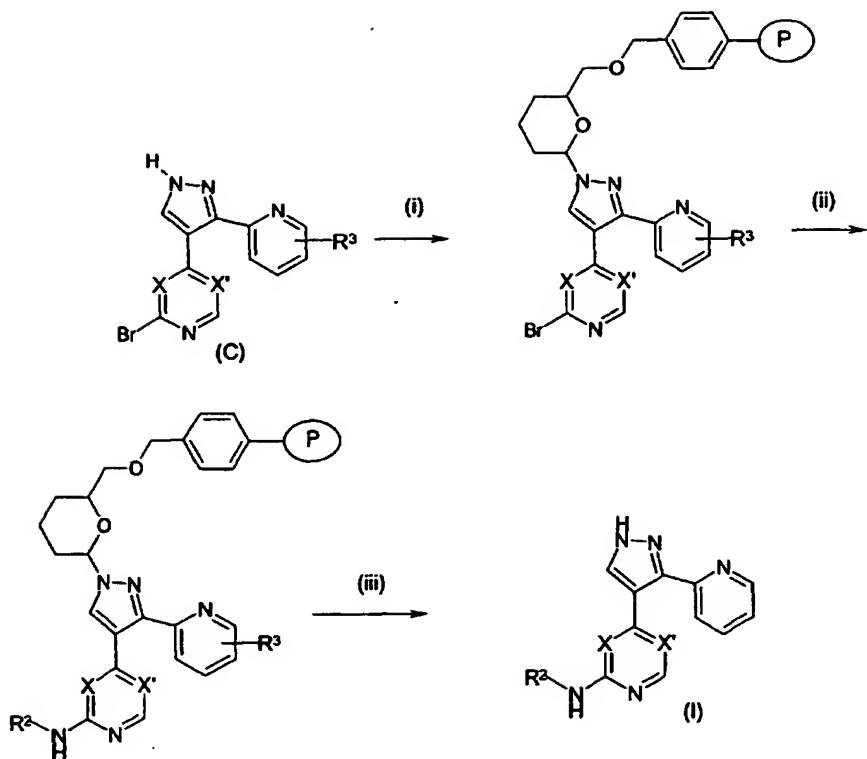
Scheme 1

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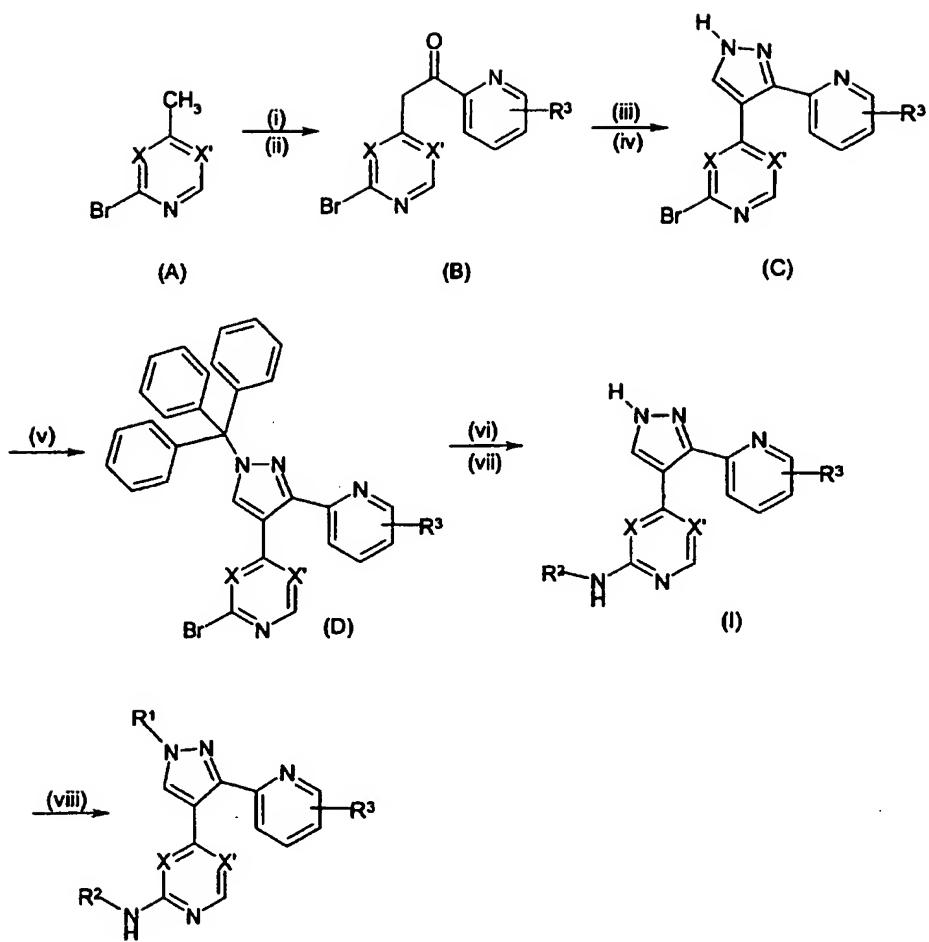
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Scheme 2



5

Reagents and conditions (preferred): (i) polystyrene DHP resin, PPTS, CH_2Cl_2 , 75°C ;
 (ii) R^2NH_2 , $\text{Pd}_2(\text{dba})_3$, binap, NaOBu^t , toluene/EtOH, 90°C; (iii) 10%TFA/ CH_2Cl_2 , r.t.

Scheme 3

5

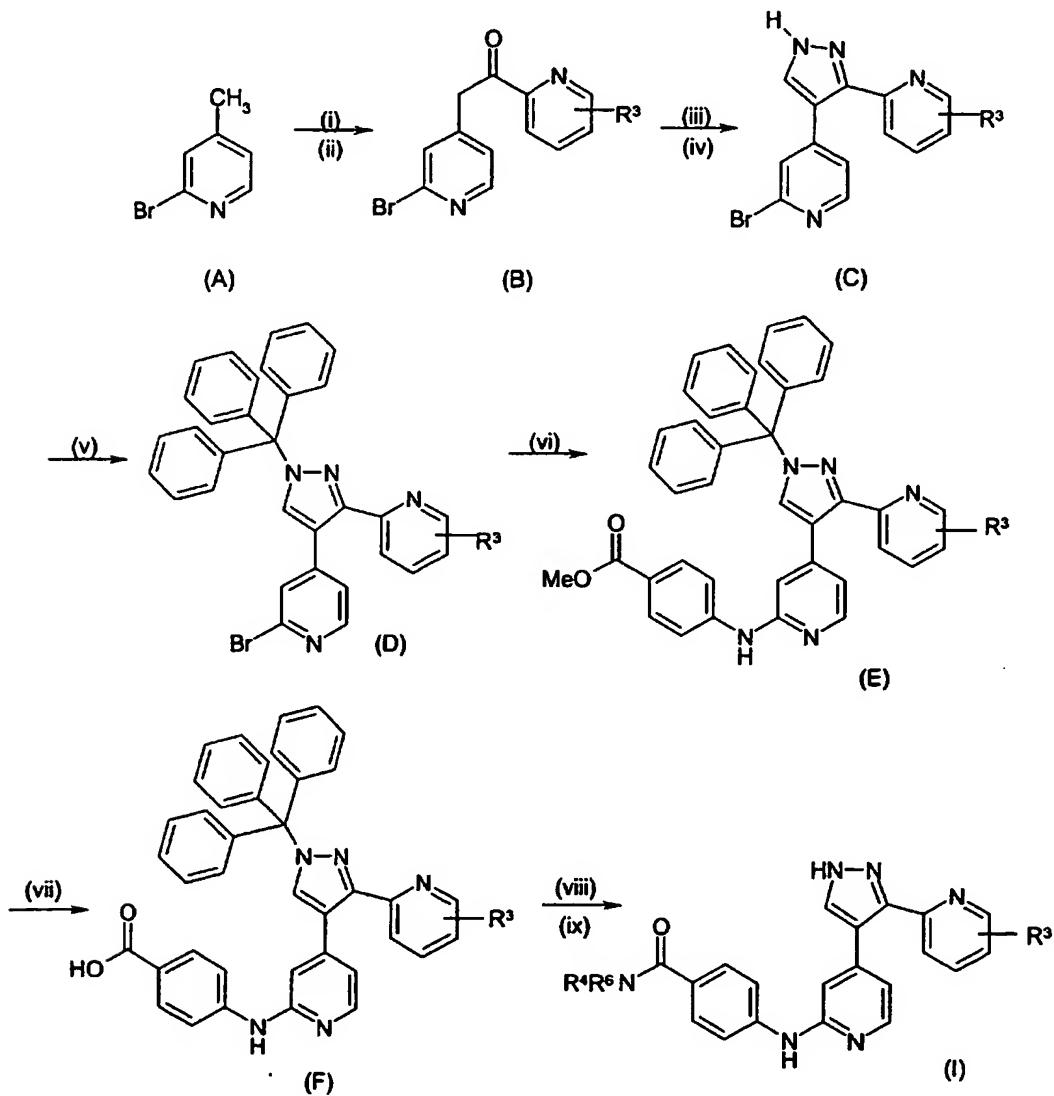
Reagents and conditions (preferred): (i) NaHMDS, THF, -50°C; (ii) R³(C₅H₃N)CO₂Et, THF, -50°C; (iii) DMF.DMA, AcOH, DMF, r.t.; (iv) NH₂NH₂.H₂O, DMF, r.t.; (v) trityl chloride, K₂CO₃ or DHP, PPTS, DCE, r.t.; (vi) R²NH₂, Pd₂(dba)₃, binap, toluene, NaOBu^t, 80°C; (vii) HCl (1N), MeOH, reflux; or TFA, CH₂Cl₂, r.t.; (viii) R¹Y, K₂CO₃, DMF, r.t.

10

Scheme 4

General synthetic pathway for compounds of formula (I), where X=X' is CH, R¹ is H and R² is phenyl substituted by CONR⁴R⁶ (where R⁴ and R⁶ are hereinbefore defined):

5



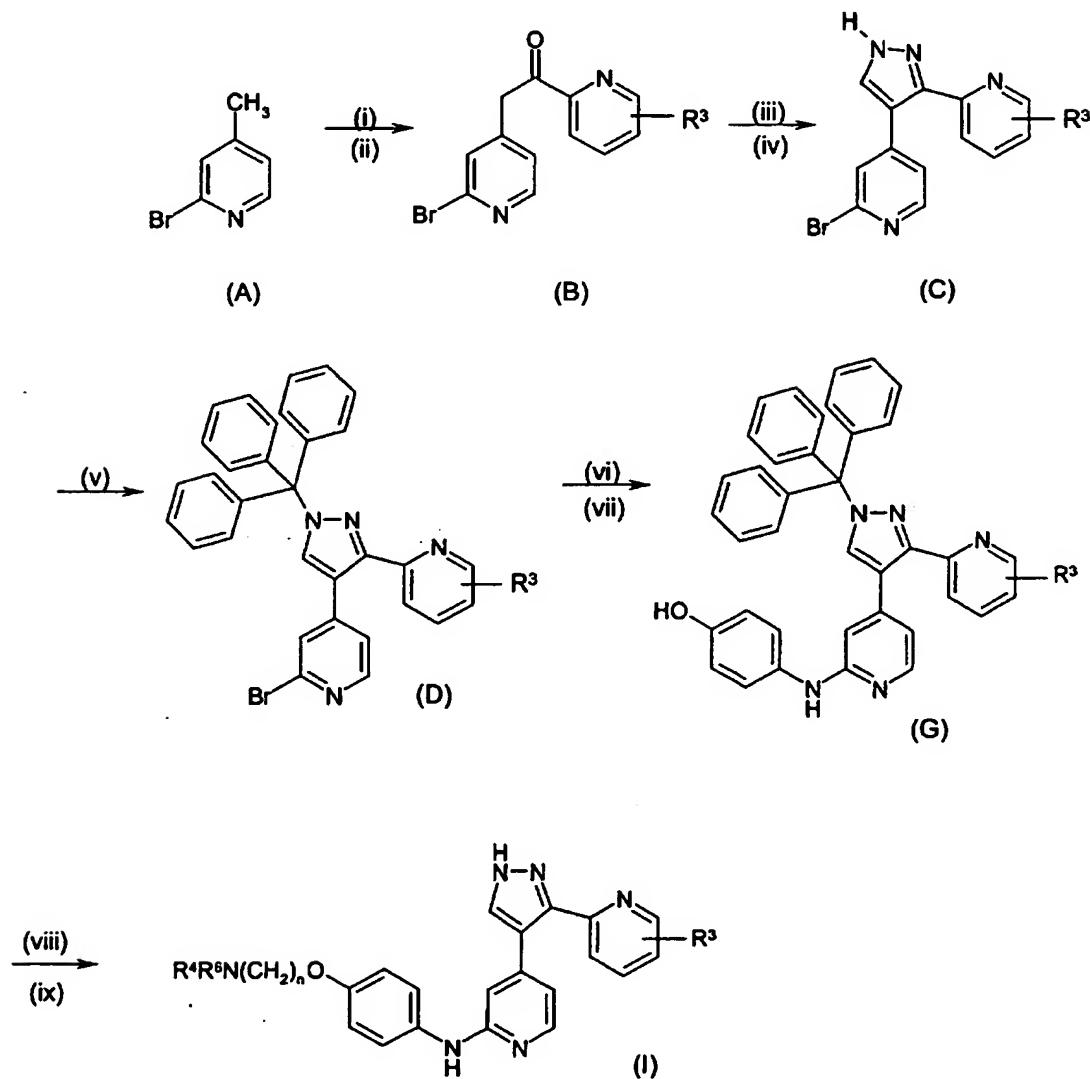
Reagents and conditions (preferred): (i) NaHMDS, THF, -50°C ; (ii) $\text{R}^3(\text{C}_5\text{H}_3\text{N})\text{CO}_2\text{Et}$, THF, -50°C ; (iii) DMF.DMA, AcOH, DMF, r.t.; (iv) $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$, DMF, r.t.; (v) trityl chloride, K_2CO_3 , acetone, reflux; (vi) 4-amino-benzoic acid, methyl ester, $\text{Pd}_2(\text{dba})_3$,

10

binap, NaOBu^t, toluene, 80°C; (vii) NaOH (1N), MeOH, reflux; (viii) R⁴R⁶NH, HOBT, EDCI, CH₂Cl₂, r.t.; (ix) HCl (1N), MeOH, reflux.

Scheme 5

5 General synthetic pathway for compounds of formula (I), where X=X' is CH, R¹ is H and R² is phenyl substituted by O(CH₂)_nNR⁴R⁶ (where n, R⁴ and R⁶ are hereinbefore defined):



10 Reagents and conditions (preferred): (i) NaHMDS, THF, -50°C; (ii) R³(C₅H₃N)CO₂Et, THF, -50°C; (iii) DMF.DMA, AcOH, DMF, r.t.; (iv) NH₂NH₂.H₂O, DMF, r.t.; (v) trityl

chloride, K_2CO_3 , acetone, reflux; (vi) 4-benzyloxy-phenylamine hydrochloride, $Pd_2(dba)_3$, binap, $NaOBu^t$, toluene, 80°C; (vii) Pd/C 10%, EtOH, 40°C; (viii) Cs_2CO_3 , acetone, R^4R^6NH , reflux; (ix) HCl (1N), MeOH, reflux.

5 List of Abbreviations

AcOH	acetic acid
Binap	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
DMF.DMA	Dimethylformamide dimethylacetal
DMF	Dimethylformamide
10 DHP	Dihydropyran
DCE	Dichloroethane
DIEA	Diisopropylethylamine
EDCL	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBT	1-Hydroxybenzotriazole hydrate
15 NaHMDS	Sodium bis(trimethylsilyl)amide
MeCN	Acetonitrile
PPTS	Pyridinium p-toluenesulfonate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
TFA	Trifluoroacetic acid
20 THF	Tetrahydrofuran
THP	Tetrahydropyran

A general process according to the invention for preparing a compound of formula (I) wherein R^1 is H, comprises:

25 (i) Addition of a suitable base, such as sodium bis(trimethylsilyl)amide or potassium bis(trimethylsilyl)amide to a substituted pyridine of formula (A), preferably in the temperature range 0 to -80°C, more preferably in the temperature range -30 to -60°C, most preferably at -50°C, in the presence of a suitable solvent such as THF;

30 (ii) Addition of a suitable monosubstituted pyridyl ester, $R^3(C_5H_5N)CO_2Et$ (wherein R^3 is hereinbefore defined) to the reaction mixture, preferably in the temperature range 0 to -80°C, more preferably in the temperature range -30 to -60°C, most preferably at -50°C, in the presence of a suitable solvent such as THF;

35 (iii) Addition of dimethylformamide dimethylacetal to the resulting ketone (B), preferably in the temperature range 0 to 75°C, more preferably in the

temperature range 20 to 60°C, most preferably at room temperature, in the presence of AcOH and a suitable solvent such as DMF; and

(iv) Addition of hydrazine monohydrate, $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$, preferably in the temperature range 0 to 75°C, more preferably in the temperature range 20 to 60°C, most preferably at room temperature, in the presence of a suitable solvent such as DMF.

It will be appreciated by a person skilled in the art that N-alkylation according to step (viii), Scherme 3 with an N-alkylating agent R^1Y (where Y is a suitable leaving group such as Cl or Br), may result in the formation of structural isomers of a compound of formula (I). Such isomers are afforded by N-alkylation of the tautomeric forms of a compound of formula (I) where R^1 is H, mentioned hereinbefore. The individual isomers and mixtures thereof are included within the scope of the present invention.

10 15 Substituted pyridine compounds of formula (A) may be prepared by processes analogous to those known in the art (e.g. Osuch et al., *J. Org. Chem.*, 1957, **22**, 939). Examples of such preparative procedures are provided in the specific examples hereinafter.

20 25 2-Bromo-4-methylpyrimidine can be prepared from 2-amino-4-methylpyrimidine (commercial) as described in the literature : Mukkala, Veli-Matti; Sund, Christian; Kwiatkowski, Marek; Pasanen, Paavo; Hoegberg, Maria; et al.; *Helv.Chim.Acta*; **75**; 5; 1992; 1621-1632.

Monosubstituted pyridyl esters, $\text{R}^3(\text{C}_5\text{H}_3\text{N})\text{CO}_2\text{Et}$ (where R^3 is as hereinbefore defined) as described in step (ii) of Schemes 1 and 3 above may be prepared by processes analogous to those known in the art. For example, where R^3 = C(6)-OMe, Finger et al., *J. Org. Chem.*, 1962, **27**, 3965; where R^3 = C(3)-OMe, Dejardin et al., *Bull. Chim. Soc. Fr.*, 1979, 289; where R^3 = C(5)-Br, Chambers and Marfat, *Synth. Commun.*, 1997, **27**(3), 515; and where R^3 = C(4)-CN, Heinisch and Lotsch, *Heterocycles*, 1987, **26**(3), 731.

N-alkylation reactions as described in step (viii), Scherme 3 may be performed according to processes analogous to those known in the art (e.g. R. Fusco, Pyrazoles, Chapter 4, p.71, *The Chemistry of Heterocyclic Compounds*, A. Weissberger (ed), Vol. 22,

Intersciences, New York, 1967 and Elguero, Pyrazoles and their Benzo derivatives, p.222, *Comprehensive Heterocycles Chemistry*, A.R. Katrisky, C.W. Rees and K.T. Potts (eds), Vol. 5, Pergamon Press, Oxford, 1984).

5 The compounds of the present invention have been found to inhibit phosphorylation of the Smad-2 or Smad-3 proteins by inhibition of the TGF- β type 1 (Alk5) receptor.

Accordingly, the compounds of the invention have been tested in the assays described herein and have been found to be of potential therapeutic benefit in the treatment and 10 prophylaxis of disorders characterised by the overexpression of TGF- β .

Thus there is provided a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as a medicament in human or veterinary medicine, particularly in the treatment or prophylaxis of disorders characterised by the overexpression of TGF- β .

15 It will be appreciated that references herein to treatment extend to prophylaxis as well as the treatment of established conditions. It will further be appreciated that references herein to treatment or prophylaxis of disorders characterised by the overexpression of TGF- β , shall include the treatment or prophylaxis of TGF- β associated disease such as 20 fibrosis, especially liver and kidney fibrosis, cancer development, abnormal bone function and inflammatory disorders.

Other pathological conditions which may be treated in accordance with the invention have been discussed in the introduction hereinbefore. The compounds of the present 25 invention are particularly suited to the treatment of fibrosis and related conditions.

Compounds of the present invention may be administered in combination with other therapeutic agents, for example antiviral agents for liver diseases, and in combination with ACE inhibitors or Angiotensin II receptor antagonists for kidney diseases.

30 According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment and/or prophylaxis of disorders characterised by the overexpression of TGF- β , particularly fibrosis.

In a further aspect there is provided a method for the treatment of a human or animal subject with a disorder characterised by the overexpression of TGF- β , particularly fibrosis, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

Compounds of the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof in admixture with one or more physiologically acceptable diluents or carriers.

There is also provided according to the invention a process for preparation of such a pharmaceutical composition which comprises mixing the ingredients.

15

Compounds of the invention may, for example, be formulated for oral, buccal, parenteral, topical or rectal administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut

oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl *p*- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

5 For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

10 Compounds of the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as
15 solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual
20 sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include
25 ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such
30 bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

5 Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

10 Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3-heptafluoropropane, 1,1,1,2-tetrafluorethane, carbon dioxide or other suitable gas.

15 Capsules and cartridges for use in an inhaler or insufflator, of for example gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

20 Compounds of the invention may conveniently be administered in amounts of, for example, 0.01 to 100mg/kg body weight, suitably 0.05 to 25mg/kg body weight orally, one or more times a day. The precise dose will of course depend on the age and condition of the patient, the particular route of administration chosen, and is entirely within the discretion of the administering physician.

25 The following non-limiting Examples illustrate the present invention.

Intermediates

30 Intermediate B1:

1-Pyridin-2-yl-2-[2-bromo-pyridin-4-yl]-ethanone

To a solution of 2-bromo-4-methyl-pyridine (27 g) in dry THF (270 ml) was added ethyl picolinate (28.5 g), the resulting mixture was cooled to -78°C under argon. A solution of sodium bis-(trimethylsilyl)amide 1M in THF (345 ml) was added dropwise at -78°C and

35 after completion the reaction mixture was allowed to warm to room temperature and

stirred overnight. The solvent was evaporated under reduced pressure and the solid residue was triturated with diethyl ether, filtered and washed with diethyl ether. The solid was then diluted with saturated NH₄Cl solution and the aqueous phase was extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated. The resulting orange powder was washed with pentane to give the title compound as a yellow solid (33.97 g).

5 m.p : 111.2°C

10 ¹H NMR (CDCl₃): δ 8.56 (d, 1H); 8.12 (d, 1H); 7.9 (d, 1H); 7.7 (td, 1H); 7.39-7.34 (m, 1H);
7.33 (s, 1H); 7.06 (d, 1H); 4.37 (s, 2H).

Intermediate B2:

2-[2-Bromo-pyridin-4-yl]-1-(6-methyl-pyridin-2-yl)-ethanone

15 2-Bromo-4-methyl-pyridine (5g, 29 mmol) and methyl-6-methylpicolinate (1.1 eq, 4.82 g, 32 mmole) were reacted as described for intermediate B1 to afford the title compound as a yellow solid (5.84 g, 70%)

MS m/z: 292 (MH⁺)

20 Intermediate C1:

2-Bromo-4-(3-pyridin-2-yl-1H-pyrazol-4-yl)pyridine

25 A solution of 1-pyridin-2-yl-2-[2-bromo-pyridin-4-yl]-ethanone (69.68 g, 0.251 mol) in dry DMF (13.5 ml) under nitrogen was treated with glacial acetic acid (2.4eq, 35 ml, 0.61 mol) over 2 min. DMF.DMA (1.5eq., 50 ml, 0.376 mol) was added dropwise and the mixture was stirred at room temperature under nitrogen for 78 min. Hydrazine monohydrate (7.5eq, 91 ml, 1.876 mol) was added dropwise, the resulting mixture was heated at 50°C for 2 h and then allowed to cool and stirred at room temperature overnight. The reaction mixture was poured into water (4 l) and extracted with ethyl acetate (1 l). The organic extracts were dried over Na₂SO₄ and filtered. Reduction in vacuo afforded a brown oil which was crystallised from acetonitrile to yield the title compound as cream solid (45.8 g, 60.5%).

30 ¹H NMR (CDCl₃): δ 8.62 (d, 1H); 8.28 (d, 1H); 7.68 (s, 1H); 7.62 (td, 1H); 7.51 (s, 1H);
7.39 (d, 1H); 7.26-7.22 (m, 2H).

Intermediate C2:2-bromo-4-(3-(6-methyl-pyridin-2-yl)-1H-pyrazol-4-yl)pyridine

2-[2-bromo-pyridin-4-yl]-1-(6-methyl-pyridin-2-yl)- ethanone (5.84 g, 20 mmol) was reacted as described for intermediate C1 to afford, the title compound as a yellow solid (3.07 g, 49%)

MS m/z: 315 (MH⁺)

Intermediate D1:2-Bromo-4-(3-pyridin-2-yl-1-trityl-1H-pyrazol-4-yl)pyridine

To a solution of 2-bromo-4-(3-pyridin-2-yl-1H-pyrazol-4-yl)pyridine (10.6 g) in acetone (200 ml) were added potassium carbonate (3eq, 14.6g) and trityl chloride (1.5eq, 14.8 g). The reaction was heated to reflux and stirred for a further 24h. After filtration, the filtrate was concentrated and then partitioned between CH₂Cl₂ and H₂O. The organic phase was dried over Na₂SO₄ and concentrated. The resulting crude material was purified by flash chromatography eluting with CH₂Cl₂/MeOH (98:2) to give the title compound as a white solid (16.3g, 85.3%), which contains the 2-trityl isomer as a minor component.

20

m.p 202°C

MS m/z 544 (MH⁺)

Intermediate D2:2-Bromo-4-[3-(6-methyl-pyridin-2-yl)-1-trityl-1H-pyrazol-4-yl]pyridine

2-Bromo-4-(3-(6-methyl-pyridin-2-yl)-1H-pyrazol-4-yl)pyridine (3.07 g, 9.8 mmol) and trityl chloride (1.5 eq, 4.1 g, 14.7 mmol) were reacted as described for Intermediate D1 to afford the title compound as the major isomer of a mixture of the two isomers, as a light yellow solid (4.9 g, 90%).

MS m/z: 558 (MH⁺)

Intermediate E:4-[4-(3-Pyridin-2-yl-1-trityl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-benzoic acid methyl ester

To a suspension of Intermediate D (5.5 g) in toluene (200 ml) were added Pd₂(dba)₃ (190 mg, 2mol%), binap (257 mg, 4mol%), 4-Amino-benzoic acid methyl ester (2.03 g, 1.3eq) and sodium tert-butoxide (1.4 g, 1.4eq). The reaction mixture was stirred at 5 80°C overnight. The mixture was poured in cold water and extracted with AcOEt. The organic layer was washed with saturated NaCl solution, dried over Na₂SO₄, filtered, evaporated to dryness and chromatographed [CH₂Cl₂/EtOH 98:2] to afford the title compound which contains the 2-trityl isomer as a minor component (3.72 g) as an orange oil.

10

Calcd. Mass for C₄₀H₃₁N₅O₂: (M + 1)⁺: 614.2556. Found (H.R.M.S): 614.2536.

Intermediate F:

4-[4-(3-Pyridin-2-yl-1-trityl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-benzoic acid

15

To a solution of 4-[4-(3-pyridin-2-yl-1-trityl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-benzoic acid methyl ester (3.72 g) in MeOH (250 mL) was added a 1 N NaOH solution (12.2 ml, 2 eq.). The mixture was stirred to reflux overnight and then the solvent was evaporated off. The residue was treated with 1 N NH₄Cl solution and extracted with AcOEt. The 20 organic layer was dried over Na₂SO₄, filtered, evaporated to dryness. The resulting powder was washed with hot MeOH to afford the title compound as an orange powder (2.88 g), which contains the 2-trityl isomer as a minor component.

Calcd. Mass for C₃₉H₂₉N₅O₂ (M + 1)⁺: 600.2400. Found (H.R.M.S): 600.2379

25

Intermediate G:

4-[4-(3-Pyridin-2-yl-1-trityl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-phenol

To a suspension of 2-bromo-4-(3-pyridin-2-yl-1-trityl-1H-pyrazol-4-yl)pyridine (4.8 g) in 30 toluene (100 ml) were added Pd₂(dba)₃ (165 mg, 2mol%), binap (222 mg, 4mol%), 4-Benzylxy-phenylamine hydrochloride (3 g, 1.4eq) and sodium tert-butoxide (2.4 g, 2.8 eq). The reaction mixture was stirred at 80°C overnight. The mixture was poured in cold water and extracted with toluene. The organic layer was washed with a saturated NaCl solution, dried over Na₂SO₄, filtered and evaporated to dryness. The resulting solid was

recrystallised from EtOH to afford the title compound (5.7 g, 97%) which contains the 2-trityl isomer as a minor component.

The mixture of the two isomers (5.7g) was dissolved in EtOH/THF (250 ml) and 5 Pd/C,10% (500 mg) was added. The reaction was stirred under an atmospheric pressure of hydrogen at 40°C overnight. The mixture was filtered through celite. The filtrate was evaporated under reduced pressure to afford the title compound, and the 2-trityl isomer as a minor component, as a brown solid after precipitation in iPr₂O(4.8 g, 97%).

10 m.p :198°C

Examples

Example 1:

(4-Chloro-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine

To a suspension of Intermediate D1 (3.15 g) in toluene (60 ml) were added Pd₂(dba)₃ (106 mg, 0.02mol%), binap (144 mg, 0.04mol%), 4-chloroaniline (890 mg, 1.2eq) and sodium tert-butoxide (780 mg, 1.4eq). The reaction mixture was stirred at 90°C overnight. The mixture was washed with diethyl dithiocarbamic acid, sodium salt 20 trihydrate (1M) and extracted with toluene. The organic layer was washed with water, dried over Na₂SO₄, filtered, evaporated to dryness and chromatographed [CH₂Cl₂ then CH₂Cl₂/MeOH 99:1] to afford 2.8 g (white solid) of 1-trityl isomer + 2-trityl isomer as a minor component.

25 The mixture of the two isomers was treated with HCl (1N)/MeOH (2/3, 100 ml) and heated at reflux for 18 h. The solvent was removed under reduced pressure and the resulting residue taken up into water and washed with CH₂Cl₂. The aqueous layer was basified with NaOH (1N, 50ml) and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and evaporated to dryness. The resulting solid was 30 recrystallised from iPrOH to afford the title compound (745 mg) as an off-white solid.

m.p :216°C

MS m/z 348 (MH⁺)

Example 2:Phenyl-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine

A procedure similar to that for Example 1 using aniline (123 mg) gave, after recrystallisation from iPrOH, the title compound as white crystals (210 mg).

5 m.p :230°C

GC-MS. 312

Example 3:(4-Fluoro-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine

10 A procedure similar to that for Example 1 using 4-fluoroaniline (444 mg) gave, after recrystallisation from iPrOH, the title compound as white crystals (380 mg).

m.p :200°C

MS m/z 332 (MH⁺)15 Example 4:Furan-2-ylmethyl-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine

A procedure similar to that for Example 1 using furfurylamine (388 mg) gave, after recrystallisation from EtOH, the title compound as white crystals (70 mg).

m.p :200°C

20 MS m/z 318 (MH⁺)Example 5:(3-Methanesulfonyl-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine

25 A procedure similar to that for Example 1 using 3-methylsulphonylaniline, hydrochloride (500 mg) gave, after recrystallisation with iPrOH/ iPr₂O, the title compound as a white solid (200mg, 27.6%).

m.p :146°C

MS m/z 392 (MH⁺)30 Example 6:3-[4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-amino]-benzonitrile

A procedure similar to that for Example 1 using 3-amino-benzonitrile (480mg) gave, after recrystallisation from iPrOH, the title compound as white crystals (515mg, 42%).

m.p :228°C

35 MS m/z 339 (MH⁺)

Example 7:2-Methoxy-4-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-amino]-benzonitrile

A procedure similar to that for Example 1 using 4-amino-2-methoxy-benzonitrile

5 (518mg) gave, after recrystallisation from MeOH, the title compound as yellow crystals (260mg).

m.p :280°C

MS m/z 369 (MH⁺)

10 Example 8:

[4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-[3-(2-piperidin-1-yl-ethoxy)-phenyl]-amine

A procedure similar to that for Example 1 using 3-(2-piperidinoethoxy)aniline (1g) gave, after recrystallisation from iPrOH, the title compound as a white powder (233mg, 16%).

15 m.p :115°C

MS m/z 441 (MH⁺)

Example 9[4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-[3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine

A procedure similar to that for Example 1 using 3-(2-pyrrolidinoethoxy)aniline (18.7 g) gave the title compound as an off-white powder (14.65 g, 49%).

m.p :141°C

MS m/z 427 (MH⁺)

25

Example 10:(3-Chloro-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine

A procedure similar to that for Example 1 using 3-chloroaniline (800mg) gave the title compound as a pale pink solid. (430mg, 49%).

30 m.p :205°C

MS m/z 348 (MH⁺)

Example 11:[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-m-tolyl-amine

m.p :250°C

MS m/z 374 (MH⁺)

Example 16:

5 4-[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-phenol

Intermediate G (400 mg) was treated with HCl(1N)/MeOH (2/3, 25 ml) and heated at reflux overnight. The solvent was removed under reduced pressure and the resulting residue taken up into water and washed with CH₂Cl₂. The aqueous layer was basified with NaHCO₃ to pH>10 and the precipitate was filtered off and washed with water. The 10 resulting solid was recrystallised from MeOH to afford the title compound (160 mg, 69%) as white crystals.

m.p :268°C

MS m/z 328 (M-1)

15

Example 17:

(4-Methoxy-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine

A procedure similar to that for Example 1 using 4-methoxyphenylamine (86.2 mg) gave, after recrystallisation from EtOH, the title compound (40 mg, 20%) as colourless 20 crystals.

m.p :219°C

MS m/z 344 (MH⁺)

Example 18:

25 [4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-p-tolyl-amine

A procedure similar to that for Example 1 using *p*-tolylamine (148 mg) gave, after chromatography [CH₂Cl₂/MeOH 95:5], the title compound (90mg, 30%) as colourless crystals.

m.p :221°C

30 MS m/z 328 (MH⁺)

Example 19:

[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-[3-trifluoromethoxy-phenyl]-amine

A procedure similar to that for Example 1 using 3-trifluoromethoxy-phenylamine (424 mg) gave, after recrystallisation from CH_2Cl_2 , the title compound (180 mg, 24.6%) as a white solid.

m.p :102.8°C

5 MS m/z 398 (MH⁺)

Example 20:

(3,4-Dimethyl-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine

10 A procedure similar to that for Example 1 using 3,4-dimethyl-phenylamine (598.11 mg) gave, after recrystallisation from MeOH, the title compound (310 mg, 25.8%) a a white solid.

m.p :220°C

MS m/z 342 (MH⁺)

15 Example 21:

[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-[4-trifluoromethyl-phenyl]-amine

A procedure similar to that for Example 1 using 4-(trifluoromethyl)aniline (90 μl , 1.2eq) gave the title compound (60 mg, 27%) as a yellow powder.

m.p :207°C

20 MS m/z 382 (MH⁺)

Example 22:

(3-Isopropoxy-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine

25 A procedure similar to that for Example 1 using 3-isopropoxy-phenylamine (290 mg, 1.3eq) gave after chromatography [$\text{CH}_2\text{Cl}_2/\text{MeOH}$ 90:10], the title compound as a yellow powder (30 mg, 12%).

m.p :218°C

MS m/z 372 (MH⁺)

30 Example 23:

(4-Methanesulfonyl-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine

A procedure similar to that for Example 1 using 4-methanesulfonyl-phenylamine (416 mg, 1.2eq) gave, after recrystallisation from iPrOH, the title compound as a yellow powder (207 mg, 26%).

35 m.p :134°C

MS m/z 392 (MH⁺)

Example 24:

2-Methoxy-4-[4-[3-(6-methyl-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-ylamino]-benzonitrile

5

A procedure similar to that for Example 1 using Intermediate D2 (3.19 g) and 4-amino-2-methoxy-benzonitrile (1.2 g) gave the title compound (1.3 g, 59.4%) as an off-white solid.

m.p :125°C

10 MS m/z 383(MH⁺)

Example 25: Morpholin-4-yl-[4-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-phenyl]methanone

15 A solution of intermediate F (1 g) in DMF was treated with HOBT (293 mg, 1.3 eq.), EDCI (401 mg, 1.3 eq.), DIEA (365 µL, 1.3 eq.) and morpholine (185 µL, 1.3 eq.). The resulting mixture was stirred for 48 hours at r.t. The solvent was evaporated off and the residue was washed with water and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and evaporated to afford the title compound (1.1g) as a colourless oil, which contains the 2-trityl isomer as a minor component . MS m/z 669 (MH⁺). The mixture of the two isomers (1.1 g) was treated with HCl (1N)/MeOH (2/3, 100 ml) and heated at reflux overnight. The solvent was removed under reduced pressure and the resulting residue taken up into 1N NaOH solution and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄, filtered, and evaporated to dryness. The resulting product was chromatographed [CH₂Cl₂/MeOH 95:5] and recrystallised from iPr₂O to afford the title compound (116 mg, 16%) as an off-white powder.

20 m.p :240°C

25 Calcd. Mass for C₂₄H₂₂N₆O₂: (M + 1)⁺:427.1882. Found (H.R.M.S): 427.1892.

Example 26: (4-Methyl-piperazin-1-yl)-[4-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-phenyl]-methanone

30 A procedure similar to that for Example 25 using Intermediate F (420mg) and N-Methyl-piperazine (100mg, 1.4 eq.) gave after recrystallisation from AcOEt, the title compound as white crystals (94 mg, 30.6%).

m.p :200°C

35 MS m/z 440 (MH⁺)

Example 27:[4-(2-Piperidin-1-yl-ethoxy)-phenyl]-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine

5 To a solution of intermediate G (400 mg) in acetone (30 mL) was added Cs₂CO₃ (1.17 g, 5.14 eq.) and 1-(2-chloroethyl)-piperidine hydrochloride (147mg, 1.14 eq.). The mixture was stirred to reflux for 48 hours and filtrated off. The filtrate was evaporated off and the residue was diluted in CH₂Cl₂ and washed with water. The organic layer was dried over Na₂SO₄, filtered and evaporated to dryness. The mixture of 1-trityl and 2-trityl
10 isomers was treated with HCl (1N)/MeOH (2/3, 30 ml) and heated at reflux overnight. The solvent was removed under reduced pressure and the resulting residue taken up into water and washed with CH₂Cl₂. The aqueous layer was basified to pH14 with NaOH (1N) and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, filtered, and evaporated to dryness. The resulting solid was recrystallised from iPrOH to
15 afford the title compound (150 mg, 48.7%) as white crystals.

m.p :176°C

MS m/z 441 (MH⁺)

Example 28:[3-(1-Methyl-1H-imidazol-2-ylmethoxy)-phenyl]-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine

A procedure similar to that for Example 27 using 2-chloromethyl-1-methyl-1H-imidazole (190 mg) gave, after chromatography [CH₂Cl₂/MeOH 95:5 then CH₂Cl₂/MeOH 90:10], the title compound (80 mg, 21.7%) an off-white solid.

25 m.p :120°C

MS m/z 424 (MH⁺)

Assays

30 Assay 1

The potential for compounds of the invention to inhibit TGF- β signaling may be demonstrated, for example, using the following *in vitro* assay.

The assay was performed in HepG2 cells stably transfected with the PAI-1 promoter (known to be a strong TGF- β responsive promoter) linked to a luciferase (firefly) reporter gene. The compounds were selected on their ability to inhibit luciferase activity after exposure to TGF- β . In addition cells were transfected with a second luciferase (Renilla) gene which was not driven by a TGF- β responsive promoter and was used as a toxicity control.

(96 well-)microplates are seeded, using a multidrop apparatus, with the stably transfected cell line at a concentration of 35000 cells per well in 200 μ l of serum-containing medium. These plates are placed in a cell incubator.

10 18 to 24 hours later (Day 2), cell-incubation procedure is launched. Cells are incubated with TGF- β and a candidate compound at concentrations in the range 50 nM to 10 μ M (final concentration of DMSO 1%). The final concentration of TGF- β (rhTGF β -1) used in the test is 1 ng/mL. Cells are incubated with a candidate compound 15-30 mins prior to the addition of TGF- β . The final volume of the test reaction is 150 μ l. Each well contains 15 only one candidate compound and its effect on the PAI-1 promoter is monitored.

Columns 11 and 12 are employed as controls. Column 11 contains 8 wells in which the cells are incubated in the presence of TGF- β , *without* a candidate compound. Column 11 is used to determine the 'reference TGF- β induced firefly luciferase value' against which values measured in the test wells (to quantify inhibitory activity) may be compared. In wells A12 to D12, cells are grown in medium without TGF- β . The firefly luciferase values obtained from these positions are representative of the 'basal firefly luciferase activity'. In wells E12 to H12, cells are incubated in the presence of TGF- β and 500 μ M CPO (Cyclopentenone, Sigma), a cell toxic compound. The toxicity is revealed by decreased firefly and renilla luciferase activities (around 50 % of those obtained in column 11).

20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 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5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 6220 6225 6230 6235 6240 6245 6250 6255 6260 6265 6270 6275 6280 6285 6290 6295 6300 6305 6310 6315 6320 6325 6330 6335 6340 6345 6350 6355 6360 6365 6370 6375 6380 6385 6390 6395 6400 6405 6410 6415 6420 6425 6430 6435 6440 6445 6450 6455 6460 6465 6470 6475 6480 6485 6490 6495 6500 6505 6510 6515 6520 6525 6530 6535 6540 6545 6550 6555 6560 6565 6570 6575 6580 6585 6590 6595 6600 6605 6610 6615 6620 6625 6630 6635 6640 6645 6650 6655 6660 6665 6670 6675 6680 6685 6690 6695 6700 6705 6710 6715 6720 6725 6730 6735 6740 6745 6750 6755 6760 6765 6770 6775 6780 6785 6790 6795 6800 6805 6810 6815 6820 6825 6830 6835 6840 6845 6850 6855 6860 6865 6870 6875 6880 6885 6890 6895 6900 6905 6910 6915 6920 6925 6930 6935 6940 6945 6950 6955 6960 6965 6970 6975 6980 6985 6990 6995 7000 7005 7010 7015 7020 7025 7030 7035 7040 7045 7050 7055 7060 7065 7070 7075 7080 7085 7090 7095 7100 7105 7110 7115 7120 7125 7130 7135 7140 7145 7150 7155 7160 7165 7170 7175 7180 7185 7190 7195 7200 7205 7210 7215 7220 7225 7230 7235 7240 7245 7250 7255 7260 7265 7270 7275 7280 7285 7290 7295 7300 7305 7310 7315 7320 7325 7330 7335 7340 7345 7350 7355 7360 7365 7370 7375 7380 7385 7390 7395 7400 7405 7410 7415 7420 7425 7430 7435 7440 7445 7450 7455 7460 7465 7470 7475 7480 7485 7490 7495 7500 7505 7510 7515 7520 7525 7530 7535 7540 7545 7550 7555 7560 7565 7570 7575 7580 7585 7590 7595 7600 7605 7610 7615 7620 7625 7630 7635 7640 7645 7650 7655 7660 7665 7670 7675 7680 7685 7690 7695 7700 7705 7710 7715 7720 7725 7730 7735 7740 7745 7750 7755 7760 7765 7770 7775 7780 7785 7790 7795 7800 7805 7810 7815 7820 7825 7830 7835 7840 7845 7850 7855 7860 7865 7870 7875 7880 7885 7890 7895 7900 7905 7910 7915 7920 7925 7930 7935 7940 7945 7950 7955 7960 7965 7970 7975 7980 7985 7990 7995 8000 8005 8010 8015 8020 8025 8030 8035 8040 8045 8050 8055 8060 8065 8070 8075 8080 8085 8090 8095 8100 8105 8110 8115 8120 8125 8130 8135 8140 8145 8150 8155 8160 8165 8170 8175 8180 8185 8190 8195 8200 8205 8210 8215 8220 8225 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processed and analysed using suitable software. The mean Luciferase activity value obtained in wells A11 to H11 (Column 11, TGF- β only) is considered to represent 100% and values obtained in wells A12 to D12 (cells in medium alone) give a basal level (0%). For each of the compounds tested, a concentration response curve is constructed from 5 which an IC_{50} value can be determined graphically.

Assay 2

The potential for compounds of the invention to inhibit the kinase Alk5 receptor may be demonstrated, for example, using the following *in vitro* assay.

The kinase domain of Alk5 was cloned and expressed in a baculovirus/Sf9 cells system.

10 The protein (amino acids 162 to 503) was 6-His tagged in C-terminus. After purification by affinity chromatography using a Ni^{2+} column, the autophosphorylation was tested. The enzyme was incubated in a medium containing : Tris 50 mM pH 7.4; NaCl 100 mM; $MgCl_2$ 5 mM ; $MnCl_2$ 5 mM ; DTT 10 mM. The enzyme was preincubated with the compounds (0.1% DMSO final in the test) 10 minutes at 37°C. The reaction was 15 initialised by the addition of 3 μ M ATP (0.5 μ Ci gamma-33P-ATP). After 15 minutes at 37°C the reaction was stopped by addition of SDS-PAGE sample buffer (50 mM Tris-HCl, pH 6.9, 2.5 % glycerol, 1% SDS, 5 % beta-mercaptoethanol). The samples were boiled for 5 minutes at 95°C and run on a 12% SDS-PAGE. The dried gels were exposed to a phosphor screen over-night. Alk5 autophosphorylation was quantified 20 using a STORM (Molecular Dynamics).

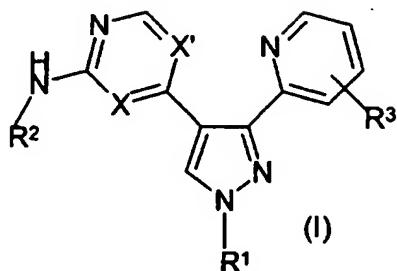
Biological Data

25 The compounds of Examples 1-28 were tested *in vitro*, using the biological assays described above. All of the compounds had an IC_{50} value of 5 μ M or below in Assay 1, and an IC_{50} value of 1 μ M or below in Assay 2.

Claims

1. 1. A compound of formula (I),

5



wherein,

R¹ is selected from H, C₁₋₄ alkyl or CH₂CONR⁴R⁵, wherein R⁴ is selected from H or C₁₋₄ alkyl and R⁵ is C₁₋₄ alkyl;

R² is selected from -(CH₂)_n-phenyl, -(CH₂)_n-heterocyclyl, -(CH₂)_n-heteroaryl, each of which may be further substituted by one or more substituents, which may be the same or different, selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁₋₄ alkyl or C₁₋₄ alkoxy, -NO₂, -NH₂, -NR⁴R⁶, -CONR⁴R⁶, -NHCOR⁴, -SO₂R⁴, -SO₂NHR⁴, -O(CH₂)_nNR⁴R⁶;

R³ is selected from H, halo, -CN, -CF₃, C₁₋₄ alkyl or C₁₋₄ alkoxy;

20 R⁴ is selected from H or C₁₋₄ alkyl;

R⁵ is C₁₋₄ alkyl;

R⁶ is selected from heterocyclyl or heteroaryl;

25 or R⁴R⁶ together with the nitrogen atom to which they are attached form a 3, 4, 5, 6 or 7 membered saturated or unsaturated ring which may additionally contain one or more heteroatoms selected from N, S or O, and wherein the ring may be further substituted

by one or more substituents selected from halo (such as fluoro, chloro, bromo), -CN, -CF₃, -OH, -OCF₃, C₁₋₄ alkyl and C₁₋₄ alkoxy;

n is 0, 1, 2, 3, 4 or 5;

5 X and X', which may be the same or different, are each selected from CH or N, provided that X and X' are not both N, and salts and solvates thereof.

2. A compound of formula (I) as claimed in claim 1, wherein R¹ is H or C₁₋₄ alkyl.

10 3. A compound of formula (I) as claimed in claim 1 or claim 2, wherein R¹ is H.

4. A compound of formula (I) as claimed in any one of claims 1 to 3 wherein n is 0 or 1.

15 5. A compound of formula (I) as claimed in any one of claims 1 to 4, wherein R³ is located at the C(3) or C(6) position of the pyridine ring.

6. A compound of formula (I) as claimed in any one of claims 1 to 5, wherein R³ is H or C₁₋₄ alkyl.

20 7. A compound of formula (I) as claimed in any of the preceding claims, wherein R⁴ and R⁶ together with the nitrogen atom to which they are attached represent pyrrolidine, pyrrolidine, imidazole, N-substituted imidazole, imidazoline, imidazolidine, pyrazole, pyrazoline, pyrazolidine, piperidine, morpholine, thiomorpholine, piperazine, N-25 substituted piperazine.

30 8. A compound of formula (I) as claimed in any one of the preceding claims, wherein R⁴ and R⁶ together with the nitrogen atom to which they are attached represent pyrrolidine, piperidine, morpholine, piperazine, N-substituted piperazine, imidazole, or N-substituted imidazole.

9. A compound of formula (I) as claimed in claim 1 selected from:

(4-Chlorophenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;

Phenyl-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;

35 (4-Fluoro-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;

Furan-2-ylmethyl-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;
(3-Methanesulfonyl-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;
3-[4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-amino]-benzonitrile;
2-Methoxy-4-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl-amino]-benzonitrile;
5 [4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-[3-(2-piperidin-1-yl-ethoxy)-phenyl]-amine; and
[4-(3-Pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-[3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine;
(3-Chloro-phenyl)-[4-(3-pyridin-2-yl)-1H-pyrazol-4-yl]-pyridin-2-yl]-amine;
10 [4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-*m*-tolyl-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-amine;
(3,4-Dimethoxy-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
(4-Chloro-3-methyl-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
15 2-Chloro-5-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-benzonitrile;
4-[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-phenol;
(4-Methoxy-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-*p*-tolyl-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-(*3*-trifluoromethoxy-phenyl)-amine;
20 (3,4-Dimethyl-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-(*4*-trifluoromethyl-phenyl)-amine;
(3-Isopropoxy-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
(4-Methanesulfonyl-phenyl)-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine;
25 2-Methoxy-4-[4-(3-(6-methyl-pyridin-2-yl)-1H-pyrazol-4-yl)-pyridin-2-ylamino]-benzonitrile;
Morpholin-4-yl-[4-[4-(3-Pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-phenyl]methanone;
(4-Methyl-piperazin-1-yl)-[4-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-ylamino]-phenyl]-methanone;
30 [4-(2-Piperidin-1-yl-ethoxy)-phenyl]-[4-(3-pyridin-2-yl-1H-pyrazol-4-yl)-pyridin-2-yl]-amine; and
[3-(1-Methyl-1*H*-imidazol-2-ylmethoxy)-phenyl]-[4-(3-pyridin-2-yl-1*H*-pyrazol-4-yl)-pyridin-2-yl]-amine;
and salts and solvates thereof.

10. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim any one of claims 1 to 9, together with a pharmaceutically acceptable diluent or carrier.

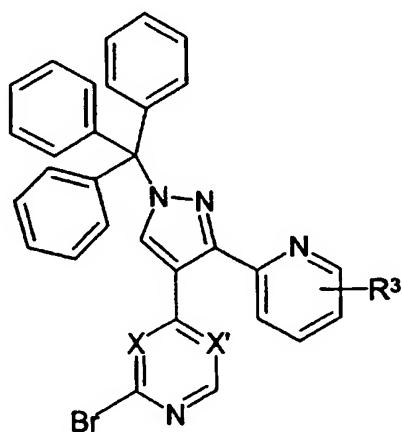
5 11. A compound of formula (I) as claimed in any one of claims 1 to 9, for use as a medicament.

12. The use of a compound of formula (I) as claimed in any one of claims 1 to 9, for the manufacture of a medicament for the treatment and/or prophylaxis of a disorder 10 characterised by the overexpression of TGF- β .

13. A method for the treatment of a human or animal subject with a disorder characterised by the overexpression of TGF- β , which method comprises administering 15 to said human or animal subject an effective amount of a compound of formula (I) as claimed in any one of claims 1 to 9 or a physiologically acceptable salt or solvate thereof.

14. A process for the preparation of a compound of formula (I) as claimed in any one of claims 1 to 9, comprising:

20 a) treatment of a compound of formula (D) with an amine R^2NH_2 in the presence of $Pd_2(dba)_3$, and binap,



(D)

wherein R^3 is defined above; and

b) subsequent removal of the protecting group from the resulting product.

5

15. A process for the preparation of a compound of formula (I) as claimed in any one of claims 1 to 9, comprising:

N-alkylation of a compound of formula (I) wherein R^1 is H, in the presence of a suitable base.

10

INTERNATIONAL SEARCH REPORT

Internat. Appl. No.
PCT/GB 00/0424A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D405/14 A61K31/444 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 12497 A (PERUMATTAM JOHN J ;DUGAR SUNDEEP (US); LIU DAVID Y (US); SCIOS INC) 9 March 2000 (2000-03-09) cited in the application abstract -----	1,10-13



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

• Special categories of cited documents :

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- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

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- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

29 April 2002

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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